

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification 6 :</b> <b>A61K 7/16</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 96/35407</b> <b>(43) International Publication Date:</b> 14 November 1996 (14.11.96)
<b>(21) International Application Number:</b> PCT/US96/06505 <b>(22) International Filing Date:</b> 8 May 1996 (08.05.96) <b>(30) Priority Data:</b> 08/439,749 12 May 1995 (12.05.95) US <b>(60) Parent Application or Grant</b> <b>(63) Related by Continuation</b> US 08/439,749 (CON) Filed on 12 May 1995 (12.05.95) <b>(71) Applicant (for all designated States except US):</b> MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> YATES, Ashley, J. [GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). KARPFF, David, B. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). <b>(74) Common Representative:</b> MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		<b>(81) Designated States:</b> AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> PREVENTION OF TOOTH LOSS BY THE ADMINISTRATION OF ALENDRONATE OR ITS SALTS  <b>(57) Abstract</b>  Alendronate, a bisphosphonate can prevent tooth loss not necessarily associated with periodontal disease. Preferably, alendronate (or a pharmaceutically acceptable salt thereof) is given daily for an extended period of time.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

- 1 -

**TITLE OF THE INVENTION****PREVENTION OF TOOTH LOSS BY THE ADMINISTRATION OF  
ALENDRONATE OR ITS SALTS****5    DESCRIPTION OF THE INVENTION**

This invention relates to a method of preventing tooth loss by the administration of alendronate or a pharmaceutically acceptable salt thereof.

**10   BACKGROUND OF THE INVENTION**

Alendronate, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid, and its pharmaceutically acceptable salts are known to be useful in the treatment of osteoporosis. See, for example U.S. Patent 4,621,077. It has also been used experimentally to treat alveolar  
15 bone loss associated with periodontitis and periodontal disease, as set forth in U.S. Patent 5,270,365.

Alveolar bone of the mandible and maxilla serves as the primary foundation for tooth support. While alveolar bone is generally subject to metabolic and other systemic diseases of the skeleton, there  
20 has been relatively little work on the occurrence, progression, or impact of systemic osteoporosis on alveolar bone, although such a relationship may exist. Mandibular bone loss has been correlated with systemic bone loss, and it has been reported that tooth loss is exacerbated by osteoporosis.

Osteoporosis of the jaw may have a relationship to tooth loss. Alveolar maxillary bone and mandibular bone may be highly susceptible to osteoporosis in those who have already lost teeth, either due to disuse or changing mechanical forces. Osteoporosis of the maxilla is accompanied by an increase in size of the paranasal sinuses,  
25 which in dentate persons can cause the maxillary antrum to extend below the roots of posterior teeth, possibly causing severe referred pain in these teeth, tooth mobility, and increased periodontal pocketing. The latter can in turn, lead to loss of crestal bone and tooth loss. If teeth are lost, many persons are now receiving dental implants, prostheses  
30

- 2 -

anchored by metal pillary in alveolar bone. Success of this process may also depend in part on the structural integrity of the bone.

Further it has been suggested that there is a relationship between periodontal disease and osteoporosis. However, it has not been  
5 shown that compounds which can treat osteoporosis may be effective in preventing tooth loss which is not associated with periodontal disease.

#### DETAILED DESCRIPTION OF THE INVENTION

This invention relates to a method of preventing tooth loss  
10 not necessarily associated with periodontal disease in a human by administering an effective amount of alendronate, or a pharmaceutically acceptable salt thereof over an extended time.

It has been found, in accordance with this invention that administration of alendronate or a pharmaceutically acceptable salt  
15 thereof to patients can result in fewer patients who experience tooth loss, as compared with patients who have not received alendronate. Further, in accordance with this invention, administration of alendronate can result in fewer numbers of teeth lost in patients receiving alendronate and who experience tooth loss, as compared with  
20 patients who do not receive alendronate. Thus another aspect of this invention is a method of lessening the risk of tooth loss by administering alendronate or a pharmaceutically acceptable salt thereof.

For purposes of this specification and claims, the following  
25 definitions apply:

Extended time: a period of time greater than two years, preferably greater than three years.

Effective amount: a dosage of alendronate (or a pharmaceutically acceptable salt thereof) required to either (a) prevent  
30 progression of osteoporosis in the mandible or maxilla so that less tooth loss occurs than in the absence of alendronate; or (b) prevent osteoporosis from occurring in the mandible or maxilla so that less tooth loss occurs than in the absence of alendronate.

- 3 -

In accordance with this invention, alendronate may be given to patients who are either suffering from osteoporosis or who do not have this underlying disease.

It may be helpful to administer alendronate or its  
5 pharmaceutically acceptable salt for an extended time in order for the beneficial effects to occur. This is particularly so for patients who are already experiencing osteoporosis, i.e. have a bone mineral density (BMD) less than about 2.0 standard deviations below the normal peak  
10 BMD. Thus, in one aspect of this invention, alendronate is administered to osteoporotic patients substantially daily for a period of greater than two years, and preferably greater than three years.

Patients preferably will receive alendronate substantially daily in order for the effect to be observable. This means that the patient will receive alendronate at least one-half of the days in a  
15 treatment period, with the treatment period lasting at least one year, and is preferably longer, up to and exceeding three or more years. In a preferred embodiment, the patient will receive alendronate substantially daily for at least three years in order to experience the greatest benefit. It is envisioned that a patient receiving such a long-term therapy may  
20 experience occasional periods when alendronate is not administered; but since alendronate has some persistent activity in the bone, this is considered within the scope of the invention provided that the patient receives alendronate at least one-half of the days in the preceding six month period. Also, it is within the scope of this invention that the  
25 alendronate be administered on a cyclical regime, i.e., the patient may receive alendronate for a given period of time, i.e., one to six months, then may be taken off the alendronate (and may or may not be given additional bone-promoting or bone absorption-inhibiting agents, and/or hormonal therapy) for a second period of time, and returned to  
30 alendronate therapy.

Alendronate may be prepared according to any of the processes described in U.S. Patents 5,019,651, 4,992,007, and U.S. Application Serial No. 08/286,151, filed August 4, 1994, each of which is hereby incorporated by reference. The pharmaceutically acceptable

- 4 -

salts of alendronate include salts of alkali metals (e.g., Na, K), alkali earth metals (e.g. Ca), salts of inorganic acids, such as HCl and salts of organic acids such as citric acid and amino acids. Sodium salt forms are preferred, particularly the monosodium salt trihydrate form.

5           The compounds of the present invention can be administered in oral dosage forms such as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, paste, tinctures, suspensions, syrups, emulsions and zydis. Likewise they may be administered in an  
10 intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be used as a tooth loss prevention agent.

          The dosage regime utilizing the claimed method is selected  
15 in accordance with a variety of factors including age, weight, sex, and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or clinician can readily determine and  
20 prescribe the effective amount of the drug required to prevent tooth loss.

          Oral dosages of the present invention will range from between 0.05 mg per kg of body weight per day (mg/kg/day) to about 1.0 mg/kg/day. Preferred oral dosages in humans may range from daily  
25 total dosages of about 2.5-50 mg/day over the effective treatment period, and a preferred amount is 2.5, 5, or 10 mg/day.

          Alendronate may be administered in a single daily dose or in a divided dose. It is desirable for the dosage to be given in the absence of food, preferably from about 30 minutes to 2 hours prior to a  
30 meal, such as breakfast, to permit adequate absorption.

          In the methods of the present invention, the active ingredient is typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier materials") suitably selected with respect to the

- 5 -

intended form of administration, i.e. oral tablets, capsules, elixirs, syrups and the like and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of a tablet or capsule, the active ingredient can be combined with an oral, non-toxic, pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol cros-carmellose sodium and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture of active ingredient(s) and inert carrier materials. Suitable binders may include starch, gelatin, natural sugars such as glucose, anhydrous lactose, free-flow lactose, beta-lactose, and corn sweeteners, natural and synthetic gums, such as acacia, tragacanth or sodium alginate, carboxymethyl cellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. A particularly preferred tablet formulation is that described in U.S. Patent 5,358,941, which is hereby incorporated by reference.

The compounds used in the instant method may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran co-polymer, polyhydroxylpropyl-methacrylamide and the like.

The following non-limiting Examples are presented to further illustrate the invention.

### EXAMPLE 1

#### Tooth Loss in Random Population

Women enrolled in this study are post menopausal, in good general health and are between 45-59 years old and have been selected randomly from a target population who live in a defined geographical

- 6 -

area. No more than 10% of the participants has any incidence of osteoporosis evident on baseline spinal dual-energy X-ray densitometry.

Each subject is randomized to either placebo, alendronate low dose (ALN 2.5 mg per day), alendronate high dose (ALN 5 mg per day) or open labeled estrogen/progestin (E/P). The estrogen/progestin group (in the United States) will receive the conjugated estrogen PREMARIN® (0.625 mg per day) and the medroxyprogesterone acetate PROVERA® (2.5 mg per day) taken continuously throughout the calendar month. Outside the United States, the estrogen/progestin group will receive micronized 17 $\beta$ -estradiol and norethisterone acetate (Trisequens) as a cyclical regimen.

All subjects who have a calcium intake of less than 500 mg per day will be advised to increase their calcium intake (either by diet or supplements) to above this level. Distribution of the groups is shown in TABLE 1. Treatment groups is given in TABLE 2.

TABLE 1

TREATMENT GROUPS

GROUP	TREATMENT	STRATUM 1		STRATUM 2		Total
		N	N/Site*	N	N/Site*	
A	Placebo	150	35-40	300	70-80	450
B	ALN** 2.5 mg	150	35-40	300	70-80	450
C	ALN 5 mg	150	35-40	300	70-80	450
D	E/P***	150	35-40	--	--	150
TOTAL		600	140-160	900	210-240	1500

\*Estimate

\*\*ALN= alendronate

\*\*\*E/P= estrogen/progestin

- 7 -

**TABLE 2****STUDY SCHEMA**

GROUP	N	1 and 2	YEAR OF STUDY	
			3 and 4	5 and 6
A	450	Placebo	Placebo	ALN* OD**; R***; and Placebo
B1	150	ALN 2.5 mg	ALN 2.5 mg	ALN 2.5 mg
B2	150	ALN 2.5 mg	ALN 2.5 mg	Placebo
B3	150	ALN 2.5 mg	Placebo	
C1	150	ALN 5 mg	ALN 5 mg	ALN 5 mg
C2	150	ALN 5 mg	ALN 5 mg	Placebo
C3	150	ALN 5 mg	Placebo	
D	150	E/P****	E/P	

5 \*ALN= alendronate

\*\*OD= Optimal Dose (either 2.5 or 5 mg).

\*\*\*R= Subsequent randomization for placebo group Years 5 and 6 extension

\*\*\*\*E/P= estrogen/pregestin

10

The study is double blind (for women receiving either alendronate or placebo) for the first two years, at the end of which a first analysis is performed. The study remains double blind until each subject reaches the end of the fourth year of study, when the blind is broken for each subject individually. Subjects are informed only whether or not they received active treatment with alendronate, and, if so, whether they were treated for two or four years. Subjects will not be informed of the dose of the study drug. Those subjects who remain in the blinded study for years 5 and 6, and the investigators remain blinded to their treatment allocation during the extension period.

20

Subjects in Group "A" (See TABLE 2) continue to take blinded placebo for four years. At the end of four years these women will be informed that they had received placebo during Years 1 to 4.

- 8 -

They are then given the option to be further randomized (1:1) between blinded placebo and alendronate at the "optimal" dose or to exit the study.

5 Groups B1 and C1 receive the 2.5 or 5 mg of alendronate, respectively for six years. Groups B2 and C2 will remain on the 2.5 and 5 mg of alendronate, respectively for four years before switching to placebo for the final two years of the study. Those subjects who remain in the study for Years 5 and 6 will be blinded (double blind) regarding their allocation to active drug or placebo for Years 5 and 6. Groups B3  
10 and C3 remain on the 2.5 and 5 mg alendronate, respectively for only two years before switching to placebo for the third and fourth years of the study. They will discontinue study drug after the fourth year.

Subjects in Group D continue the open label estrogen/progestin treatment for four years, after which they will  
15 discontinue the study drug after the fourth year.

At the first visit, a member of the study staff performs an oral examination which includes a tooth count in each patient. A similar examination is conducted after 24 months, and every two years thereafter for the remainder of the study.

20 Fewer patients receiving alendronate (either high dose or low dose) experience tooth loss as compared to controls receiving placebo. Additionally, for those patients who do experience tooth loss, fewer teeth are lost by those receiving alendronate than those receiving placebo. These differences are statistically significant.

25

## EXAMPLE 2

### Tooth Loss in Osteoporotic Population

This trial is conducted similarly to that described in  
30 Example 1, except that the approximately 2,400 women who are participants are osteoporotic, i.e. have a bone mineral density less than 2.0 standard deviations below peak mean bone mass. Approximately 33% of the patients have a prevalent vertebral fracture at baseline. Randomization is split between placebo and alendronate. The dose of  
35 alendronate is 5 mg per day for the first two years, and 10 mg per day

- 9 -

for the third year. All subjects who have a calcium intake less than 1,000 mg per day are offered free calcium supplements which provide 500 mg elemental calcium and 250 units of vitamin D.

- 5 After three years, fewer patients receiving alendronate experience tooth loss than those receiving placebo. Additionally, for those patients who do loose teeth, fewer teeth are lost by those receiving alendronate than those receiving placebo.

- 10 -

WHAT IS CLAIMED IS:

5           1.     A method of preventing tooth loss not necessarily associated with periodontal disease comprising administering to a patient an effective amount of alendronate, or a pharmaceutically acceptable salt thereof for a substantial period of time.

10           2.     A method according to Claim 1 wherein the alendronate is in the form of monosodium alendronate trihydrate.

          3.     A method according to Claim 1 wherein the alendronate or its pharmaceutically acceptable salt is administered orally.

15           4.     A method according to Claim 3 wherein the dosage is 2.5 mg/day to 40 mg/day.

          5.     A method according to Claim 4 wherein the dosage is 2.5, 5, or 10 mg/day.

20           6.     A method according to Claim 5 wherein the alendronate is administered substantially daily for at least about 3 years.

## INTERNATIONAL SEARCH REPORT

 International application No.  
 PCT/US96/06505
**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : A61K 7/16

US CL : 424/49, 57; 514/902, 108

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/49, 57; 514/902, 108

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,270,365 A (B. GERTZ ET AL.) 14 December 1993 (14.12.93), column 1, lines 4 to 21.	1-6
A	US 4,621,077 A (S. ROSINI ET AL.) 04 November 1986 (04.11.86).	1-6
A	US 5,366,965 A (K. STREIN) 22 November 1994 (22.11.94), column 4, lines 36-37.	1-6
A, P	US 5,431,920 A (S. BECHARD) 11 June 1995 (11.06.95), column 1, line 50.	1-6
A, P	US 5,462,932 A (G. BRENNER ET AL.) 31 October 1995 (31.10.95).	1-6

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A document defining the general state of the art which is not considered to be of particular relevance	*X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E earlier document published on or after the international filing date	*Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A document member of the same patent family
*O document referring to an oral disclosure, use, exhibition or other means	
*P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

24 JULY 1996

Date of mailing of the international search report

09 AUG 1996

 Name and mailing address of the ISA/US  
 Commissioner of Patents and Trademarks  
 Box PCT  
 Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

SHEP K. ROSE jd

Telephone No. (703) 308-1235